LONI Visualization Environment

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Over the past decade, the use of informatics to solve complex neuroscientific problems has increased dramatically. Many of these research endeavors involve examining large amounts of imaging, behavioral, genetic, neurobiological, and neuropsychiatric data. Superimposing, processing, visualizing, or interpreting such a complex cohort of datasets frequently becomes a challenge. We developed a new software environment that allows investigators to integrate multimodal imaging data, hierarchical brain ontology systems, on-line genetic and phylogenetic databases, and 3D virtual data reconstruction models. The Laboratory of Neuro Imaging visualization environment (LONI Viz) consists of the following components: a sectional viewer for imaging data, an interactive 3D display for surface and volume rendering of imaging data, a brain ontology viewer, and an external database query system. The synchronization of all components according to stereotaxic coordinates, region name, hierarchical ontology, and genetic labels is achieved via a comprehensive *BrainMapper* functionality, which directly maps between position, structure name, database, and functional connectivity information. This environment is freely available, portable, and extensible, and may prove very useful for neurobiologists, neurogeneticists, brain mappers, and for other clinical, pedagogical, and research endeavors.

KEY WORDS: Software, ontology, brain, atlas, visualization, gene mapping

INTRODUCTION

General

Contemporary brain mapping research¹ involves integrating imaging data with behavioral, genetic, neurobiological, and neuropsychiatric data. The complexity of the data introduces challenges in its modeling, computational processing, and visualization. To address these problems, we developed

the Laboratory of Neuro Imaging Visualization Environment (LONI Viz). This environment allows integration of multimodal imaging data, hierarchical brain ontology systems, on-line genetic and phylogenetic databases, and 3D virtual data modeling.² There are four main components of LONI Viz: a (three-way cardinal projection) sectional viewer for imaging data, an interactive 3D display for surface and volume rendering of imaging data, a brain ontology viewer, and an external database query system. These components are synchronized using a *BrainMapper*, which directly maps between anatomical position, structure name, database, and functional connectivity information. The LONI Viz environment is useful for training and education purposes as well as for research and clinical applications requiring visual inspection and interrogation of multimodal, multidimensional and multiformat brain data.

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Other Similar Efforts

Over the past several years, a number of new software tools have surfaced that allow interactive brain data filtering, visualization, and analysis. Most of these packages prove extremely practical for the specific applications they are designed for (e.g., *MultiTracer*³). Few provide the foundation for multiformat data integration, interactive modeling, data mining, and interfacing external dynamic databases. Table 1 summarizes the major software developments in the field computational and graphics-based neuroscience and brain mapping.

Brain Mapping

Contemporary brain-mapping studies involve processing an increasingly large and complex data,

and utilization of advanced statistical techniques; and require interactive real-time data integration, presentation, and visual inspection. Brain data can originate from multiple imaging modalities (e.g., MRI, immunohistochemistry), be stored in various formats (e.g., volumetric, metadata) and interrogated by using different (studies/species specific) processing protocols. For example, investigators need to dynamically analyze, correlate, and visualize white matter diffusion anisotropies, behavioral/stress alterations, and genetic comorbidity associated with specific regions in the mouse brain. A number of software tools have been developed to address individual needs in terms providing the computational infrastructure to address one or several of these challenges.⁴ Few attempts have been instantiated into integrating brain atlas construction,^{5,6} 3D object modeling,^{7,8} neurogenetics, and biostatistics.^{9,10}

Table 1. State-of-the-art software packages for data integration, processing and visualization

Software	Institution	URL	Brief Description
FreeSurfer	Harvard University	http://surfer.nmr.mgh.harvard.edu/	3D Surface modeling & visualization
FisWidgets	University of Pittsburgh	http://neurocog.lrdc.pitt.edu/fiswidgets/	Java graphical compute environment
SPM	University College, London	http://www.fil.ion.ucl.ac.uk/spm	Suite of tools for stat analysis and visualization
BrainVoyager	Brain Innovation, Inc.	http://www.brainvoyager.com/	Brain visualization, simulation and analysis
BrainImagingToolbox	MNI, McGill University	http://www.bic.mni.mcgill.ca/software	Brain data processing, display and analysis
VisDB	University of Munich	http://www.dbs.informatik.uni-muenchen.de/dbs/projekt/visdb/visdb.html	Visual data mining
Brainiac	Medical Multimedia Systems	http://www.webcom.com/medmult/brainiac.html	Interactive brain Atlas
MRlcro	University of Nottingham	http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html	Versatile 3D modeling & visualization environment
ImageJ	NIH	http://rsb.info.nih.gov/ij/	Image processing/visualization
IDL	Research Systems, Inc.	http://www.rsinc.com/idl/	Interactive data processing/viz
MRI3DX	Aston University	http://www.aston.ac.uk/lhs/staff/singhkd/mri3dX/	Integrated tool for visualization and analysis
Amira	TGS, Inc.	http://www.amiravis.com/	State-of-the-art visualization and data modeling package
AVS	Advanced Visual Systems	http://www.avs.com/	Visualization application and development environment
Khoros	Khoros, Inc.	http://www.khoros.com/khoros/toolboxes/	Information processing, data exploration and visualization
MedX	Sensor Systems, Inc.	http://medx.sensor.com/	Multimodal image processing, visualization and analysis
Vis5D	University of Wisconsin	http://vis5d.sourceforge.net/	Space/time/function 5D viewer
MultiTracer	UCLA	http://air.bmap.ucla.edu/MultiTracer/MultiTracer.html	3D Viewing & delineation tool

APPROACH AND METHODS

The type of brain visualization environment that we seek requires a number of synchronized functions organized in a graphical, user-friendly, platform-independent, and well-documented software package.^{11–13} The LONI Viz environment consists of several independent components, dynamically linked via a functional wrapper called BrainMapper. Each of these modules is described in detail below. We demonstrate the functionality of the LONI visualization environment using the LONI Mouse Brain Atlas.¹⁴ The atlas contains imaging data (MRI, cryotomographic, Nissl stain, and labeled volume),¹⁵ a *BrainGraph* model,¹⁶ and a *BAMS* relational database.^{17,18} The latter contains genetic, referential, and contextual metadata, which is used to establish communication between the imaging displays, the *BrainGraph* viewer, and the external databases.

Sectional Image Viewer

This component of LONI Viz provides a standard radiologic reference frame for displaying cardinal projection/section planes of 3D data (e.g., structural and functional data as well as statistical significance maps). Axial, sagittal, and coronal views are simultaneously displayed and synchronously controlled by the investigator by cursor drag-and-drop functionality (Fig. 1). This framework allows the superposition of multiple volumes, modalities, selection of stereotaxic coordinates, and reports the regional ontology labels. Both voxel and world-space coordinates as well as volume intensities and

histograms are provided in this component of the LONI Viz environment. A number of image enhancing tools (e.g., battery of color maps, zooming, panning, contrast/brightness filters, etc.) are provided to aid the user in displaying and identifying features of interest. This type of visualization is common for most 3D imaging tools and we have designed our own to address a number of issues in current software related to limited file-format parsing, computer architectures and system requirements, and static interfaces.

BrainGraph Ontology Viewer

Many neuroanatomical labeling schemes differ significantly in their hierarchical nomenclature organization. There are developmental cephalic organizations where the brain is separated, or tessellated, into anatomically disjoint regions based on the cellular lineage.¹⁹ There also exist neurolabeling approaches that systematically organize the hierarchy of structures based on cytoarchitectonic,²⁰ functional,²¹ or chemoarchitectonic connectivity.²² And there are variations within each of these schemes, differences in naming between research groups and studies.²³ For example, an investigator devising a study that uses the Paxinos labeling scheme²⁴ may desire cross-validation with studies utilizing Swanson hierarchical nomenclature.²³

Initially, we developed a tree-based hierarchical data structure, *BrainTree*, to address the need for linking anatomical, functional, and contextual neuroscientific information. The *BrainTree* approach was successfully used in conducting both volumetric studies²⁵ and functional activation studies²⁶ in Alzheimer's disease neuroimaging data. The *BrainTree* data

Fig 1. LONI Viz Sectional Viewer shows cardinal projection planes in the axial, sagittal, and coronal orientation.

model introduced the following: graphical and interactive organization of brain anatomy; a common coordinate-to-label reference frame; linking neuroimaging, neurogenetic, neuropsychiatric, and contextual data; hierarchical representation of neuroanatomical names in an accessible and user-friendly manner; region anatomical location (containment by, and of, other neighboring regions); an extremely conceptually and computationally attractive data representation (tree structure).

In the original BrainTree, we used a tree-based, relational data model because storing, retrieving, and manipulating tree structures is well understood²⁷ and computationally tractable. Eventually, we found that the tree structure was limited in its scope because in many situations different paths exist between two remote structures that are not necessary descendants of each other. To address these limitations, we extended the BrainTree as a general, flexible, graph-based data model, and the BrainGraph, which integrates, organizes, and provides direct access to external structural, functional, histological, genetic, and contextual brain information. Because pure hierarchical organizations based on anatomical containment are insufficient to represent complex circular, dynamic, and study-specific interrelations between different regions in the brain, the BrainGraph is required to provide this functionality (Fig. 2). It allows the simultaneous storage of multiple ROI labeling schemes, and provides study-specific graph traversal schemes. In this system, each node (ROI) and each edge (connection link) has a number of predefined (or user specifiable) description categories (e.g., functional connectivity, anatomical relations to its neighbors, developmental information, genetic information, literature references, and other external contextual information).

3D Volume & Surface Viewer

A truly three-dimensional brain atlas should allow the investigators to (1) freely move about in space, (2) detect morphological shape, size, and position, and (3) retrieve, traverse, or store metadata for specific regions (or voxels) in the brain. To address this requirement, we designed a virtual 3D object viewer that renders brain anatomy, contour, surface, and label objects, and provides the means of cutting, measuring, and superimposing auxiliary brain data in the 3D scene. A local and a global coordinate system, zooming, panning, and morphometric capabilities provide an easy interactive access to stereotaxic brain data, surface models, and brain ontology (Fig. 3).

External Database Viewer

Access from the LONI Viz environment to remote neurophylogenetic, neurogenetic, and ontology databases is provided via a database traversal engine. Currently, we have direct database query links to Jackson Laboratories Mouse Database,²⁸ NIH Database,²⁹ GeneOntology (GO) Consortium,³⁰ GeneSat Database,³¹ and Brain Architecture Management System (BAMS).^{18,32} Selecting a 3D anatomical voxel or a region of interest in any LONI Viz component triggers an automated query for the metadata associated with the specific structure (Fig. 4). The results typically contain gene-expression signatures, functional connections, literature references, and ontology relations to other structures, and are displayed in HTML tabular format using the default system browser.

Fig 2. BrainGraph is a hyperbolic display of brain ontology systems. Insert in the left shows textual elds saved for each ROI.

Fig 3. 3D Surface and Volume Renderer displays surface models, volumetric ROI renderings, and allows oblique sectioning of the virtual scene.

Fig 4. Database Viewer displays externally obtained HTML summaries of homologies, genetics, and anatomical contexts obtained from external databases.

Synchronization Component: BrainMapper

The four LONI Viz components described above are designed and implemented as stand-alone brain imaging applications. The entire suite of them, however, provides the framework for dynamic data interrogation, complex visualization, and multimodal data integration. The challenge of establishing a robust link between these independent modules was resolved by engineering a communication protocol (BrainMapper) (Fig. 5). The main interaction messages relayed between the individual components through the BrainMapper consist of the quadruple vector of location, label, ontology, and action. Every component is both a listener and an event generator to send and react to messages specific to its feasibility domain. The BrainMapper functionality uses *propertyChange* firing/listening mechanisms to establish synchronization between different components and widgets.

LONI Atlas Transformation and Information Server

Often, medical images contain extremely high-resolution data that may exceed 1 GB in size (e.g., cryotomographic and immunohistochemistry data). This makes it impractical to locally store the entire dataset at runtime. To accommodate these needs, we have developed an atlas transformation and information server (LATIS) that allows LONI Viz, and other applications, to retrieve high-resolution imaging data over the Internet. The server provides a flexible protocol for interfacing

and requesting small sections or volumes from a very high-resolution dataset (an atlas) via a web-server HTTP. Figure 6 illustrates the functionality of the LATIS–LONI Viz communication in providing additional high-resolution data from the LATIS server to client (LONI Viz). The user manually selects a rectangular region of interest in one of the cardinal projection planes. The LATIS server sends a high-resolution image of the region, which can further be magnified using LATIS services.

DISCUSSION AND FUTURE DIRECTIONS

Advantages of using LONI Viz

The LONI Viz environment is designed and implemented as a lightweight Java interface to multimodal brain data. It can be used for visual and quantitative analysis of neuroscientific data with or without an anatomical brain atlas. Most of its functionality, however, is utilized when the full spectrum of imaging and metadata are available. The LONI Viz's real-time 3D data display and interactive synchronization between local and remote neuroscience resources make it attractive for researchers and educators, because at each

Fig 5. BrainMapper is a synchronizing agent that modulates the communication between the four main components of the LONI Viz environment. It ensures a match between stereotaxic coordinates, region labels, hierarchical representation, and database communication.

Fig 6. LATIS Server provides on-the-fly high-resolution neuroimaging data over HTML protocols to LONI Viz.

time and space location it provides the answers to questions like such as: Where are we? What is known about the region? What pathways pass through the region? What gene patterns are known for the region? Layer controls (Fig. 7) allow the efficient juxtaposition of a multitude of data volumes, labels, and ontology systems. With its dynamic linking and expansion features, the LONI Viz environment becomes a foundation for advanced neuroinformatics research based on the direct access to imaging, genetics, homology, and metadata.

Availability

The current version (v. 5.0) of the LONI visualization environment is available as a platform-independent Java binary package. We also provide the source code on a collaborative basis. It can be downloaded from our web page (http://www.loni.ucla.edu/Software/Software_Detail.jsp?software_id=7). On-line development tools, class UML diagrams, user manuals, snapshots, bug-tracking reports, and feedback forms are also available at this page.

LONI Viz architecture

The LONI visualization environment is built with a small kernel of core interfaces where functionality is provided by plug-ins and object extension. The entire package is purely implemented in the Java programming language to ensure maximum portability across hardware platforms. Basic Java 1.4+ virtual machine, Java3D (both are freely available from <http://java.sun.com/>), and Internet connection are required for complete the functionality of LONI Viz. A typical user will just download and uncompress the zip archive from our download page and run one of the JAR, BAT, or CSH scripts to start the application. No installation or configuration is required, provided the Java virtual machine and Java 3D are properly installed on the system. Some known problems include old versions of Java on SGI IRIS and Apple Macintosh systems. We strongly recommend 512 MB+ RAM memory to best utilize the software in terms of speed, performance, and functionality. The LONI Viz system architecture is available on-line at http://www.loni.ucla.edu/download/LOVE/LOVE_UML.gif.

Fig 7. In LayerControls, different color maps are selected to enhance the distinction between the four different imaging modalities simultaneously loaded and superimposed in LONI Viz.

Neuroinformatics

Bioinformatics is the science of representation, modeling, analysis, and interpretation of large amounts of intricate biomedical data. Neuroinformatics is the subfield restricting these studies to the central nervous system. The LONI Viz environment allows us to conduct neuroinformatics studies by integrating neuroimaging, neurogenetics, neuroontology data, and computational modeling, and providing a brain mapping functionality for associating changes in one dataset as functions of changes in the others. The most straightforward example is interrogating the genotypic (e.g., gene expression rates), phenotypic (e.g., cognitive tests, disease, age), and neuroimaging pathology in studying cortical thinning³³ or alterations in neurometabolism³⁴ in dementia.

Interactive In Situ registration and 3D Reconstruction

It is a common challenge in neurobiology to reference cytoarchitectonic and immunohistochemical coordinates, gene expression maps (location,

intensity, and function), and remote neural networks in the brain. To address this problem, we are currently developing a semiautomated technique to coregister an arbitrary-plane-of-section of an *in situ* hybridization or stained 2D image slice to a fully 3D brain atlas. This will involve a two-stage approach where the user first virtually positions the raw slice into its approximate orientation, and then a finer automated alignment completes the registration by minimizing a certain cost function.³⁵ Such functionality will eliminate the difficulty of contrasting and integrating data, atlases, and image modalities obtained by using different image acquisition protocols (e.g., different orientations, variable slice thicknesses, contrasts, resolution).

Extensible Plug-in Architecture

The LONI Viz environment is designed in a plug-in architecture (e.g., tools, color maps, volume parsers). Using a plug-in architecture, we are currently designing a new interface to the LONI Viz environment that would allow the efficient development and deployment of new data- and project-specific bioinformatics and data-mining

Fig 8. An example of a LONI Viz tool plug-in: semiautomated segmentation of regions of interest using SOCR EM algorithm. Left: The manual region outlining functionality and the resulting superposition of the result of the EM mixture modeling segmentation of the region. Right: Decomposition of the region intensity distribution to a mixture of three Gaussian densities (user has control over the mixture parameters).

tools. This will include length, area, and volume calculators, temporal correlation analyses, methods for linear modeling, and statistical inference. An example of the image processing plug-in is an image segmentation tool (Fig. 8). This tool utilizes the *expectation maximization* estimation model, available via the Statistics On-line Computational Resource.³⁶ It allows us to segment any free-drawn shape interactively by fitting a mixture of several Gaussian models for the different brain tissue types. Areas of each tissue type may be exported and saved in an external file for further computational analysis (e.g., measuring hippocampal volume across subjects or time).

Contour/Surface Modeling

Some 3D brain display programs already allow interactive region or cortical delineation or surface reconstruction.³⁷ Obtaining models of cortical and limbic system objects and accurate representations of sulcal and gyral anatomy is crucial in identifying disease pathogens,³⁸ developmental abnormalities (e.g., asymmetries, group variabilities),³⁹ and normal aging.⁴⁰ We are currently developing the LONI Viz infrastructure for interactive delineation of structures, 3D curve drawing, and statistical analysis of the resulting shapes. A generic shape viewer is already devel-

oped and is currently configured as a display plug-in for LONI Viz (http://www.loni.ucla.edu/CCB/Software/Software_Detail.jsp?software_id=18).

4D Temporal Visualization

Temporal patterns and characteristics of functional MRI and structural longitudinal MRI studies are extremely important in identifying neuronal networks,⁴¹ disease progression,⁴² growth,⁴³ and atrophy^{44,45} in the brain. Visualizing such temporal effects is often times reduced to tensor maps⁴⁶ or other static displays.⁴⁷ We are developing the framework for dynamically interrogating and viewing such 4D volumes and correlating this imaging data with their corresponding auxiliary neurodescriptions.

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